UNITED STATES DISTRICT COURT
WESTERN DISTRICT OF LOUISIANA
LAFAYETTE DIVISION

IN RE: ACTOS (PIOGLITAZONE) PRODUCTS LIABILITY LITIGATION

MDL No. 6:11-md-2299

This Document Applies To:
Allen, et. al. v. Takeda Pharmaceuticals North America, Inc., et al.
(Case No. 12-cv-00064)

JUDGE DOHERTY

MAGISTRATE JUDGE HANNA

MEMORANDUM RULING:
DEVELOPMENT OF BLADDER CANCER WITHIN ONE YEAR OF EXPOSURE

This multidistrict litigation arises from product liability claims against the manufacturer and marketer of Actos® and other drugs containing pioglitazone. Pending before this Court is the Defendants' Motion to Exclude Testimony of Plaintiffs' Experts that Actos® can Cause Bladder Cancer Within One Year of Use,[1] in which the Defendants seek to exclude testimony by several of the Plaintiffs' experts. Because of the importance of this motion, this Court heard oral argument on December 12, 2013, and that argument will, also, be addressed herein.

EVIDENCE AT ISSUE

Mr. Allen alleges he has experienced bladder cancer, specifically, urothelial carcinoma of the bladder, which is a tumor in the urothelial lining of the bladder, and that this cancer was caused in substantial part by pioglitazone developed and sold by "the Defendants."[2] The Plaintiffs intend to present testimony on general causation from the following experts at the trial of this matter:

[1] Rec. Doc. 3466. This motion has been urged on behalf of all named defendants in this matter.

[2] For these purposes only, the Court will not distinguish among the Defendants as it is not legally significant to the issues at hand.

- Dr. Martyn Smith (toxicologist)
- Dr. Jennifer Southgate (molecular biologist)
- Dr. Dipak Panigrahy (cancer biologist)
- Dr. Sebastian Schneeweis (epidemiologist)
- Dr. Herbert Grossman (urologist)
- Dr. Scott Delacroix (urologist), and
- Dr. David Madigan (statistician)

These experts, collectively, will present a theory of general causation as to how Actos® is allegedly capable of causing and/or "promoting," i.e., causing to progress more quickly than would be normal, bladder cancer in humans, and that the effects can begin within one year of exposure. The Defendants challenge the factual correctness of the Plaintiffs' theory of causation, along with the admissibility of all evidence supporting this theory, along with the theory itself. Their admissibility challenge focuses solely on the reliability of the experts' methodology and conclusions; the Defendants do not challenge these experts' qualifications, but for Dr. Madigan.[3]

The foundational disagreement between the parties is focused on the proper interpretation of data from a number of studies and the distinction between the underlying foundational aspect of the theory and the theory itself. The Plaintiffs believe the data support the conclusion that Actos® causes or promotes bladder cancer in humans, while the Defendants believe the data cannot support this conclusion and each rely upon a theory of causation to support their position. The Defendants' motion asks the Court, in its role as gatekeeper, to exclude the Plaintiffs'

[3] Defendants challenge Dr. Madigan as being unqualified to testify Actos® causes bladder cancer within one year, arguing he lacks specified knowledge and did not conduct an independent investigation. However, as discussed *infra,* neither Dr. Madigan's report nor Plaintiffs' arguments suggest that Dr. Madigan will offer such an opinion.

evidence and theory at trial. The Defendants' argument for excluding the evidence and theory is as follows:

- it is not possible for bladder cancer to develop within one year of exposure to any carcinogen;
- the human studies relied upon by the Plaintiffs do not exclude bladder cancers that developed within one year of exposure, so the results of those studies are flawed and, if this flaw were corrected, the studies would show no statistical association between Actos® and bladder cancer in humans;
- therefore, the Plaintiffs' theory is unreliable and incorrect.

Because the Plaintiffs' experts are not without support by methods, principles, and analyses, not shown to be scientifically unsound, and because the foundational assumption and theory underpinning Plaintiffs' experts are not so flawed as to, in and of themselves, be inadmissible and as the basis of argument within of the Defendants' motion i.e., that bladder cancer cannot develop within one year of exposure, is highly contested, and because the Defendants have not demonstrated, as they argue, that the Plaintiffs' theory is biologically implausible, or otherwise the result of "pseudoscience", and for the full reasons delineated below and discussed at oral argument held on December 12, 2013 and placed into the record at that time, and herein adopted and incorporated into this ruling, the Defendant's motion is DENIED and Plaintiffs will be permitted to present their theory and the challenged evidence to the jury.

LAW AND ANALYSIS

I. APPLICABLE LAW

While state law governs the Plaintiffs' claims in this matter, the Federal Rules of Evidence control the admission of expert testimony.[4] Under the Federal Rules of evidence,

[4] *Huss v. Gayden*, 571 F.3d 442, 452 (5th Cir. 2009), *citing Mathis v. Exxon Corp.*, 302 F.3d 448, 459 (5th Cir. 2002).

"relevant" evidence is admissible, while irrelevant evidence not admissible.[5] Evidence is "relevant" if it has any tendency to make a fact more or less probable than it would be without the evidence, and the fact being proven or disproven is of consequence in determining the action.[6] The party seeking to have expert opinion evidence admitted into evidence bears the burden of demonstrating, by a preponderance of the evidence, that the expert's findings and conclusions are based on the scientific method and, therefore, are reliable.[7]

The Federal Rules of Evidence require that a judge, faced with a proffer of expert scientific testimony, must begin by determining, pursuant to Rule l04(a), whether the expert is proposing to (i) testify to scientific knowledge (ii) that will assist the trier of fact to understand or determine fact in issue.[8] This will require a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology properly can be applied to the facts in issue.[9] This requirement is found in Rule 702 of the Federal Rules of Evidence, which reads as follows in its entirety:

> A witness who is qualified as an expert by knowledge, skill, experience, training, or education may testify in the form of an opinion or otherwise if:
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> (a) the expert's scientific, technical, or other specialized knowledge will help the trier of fact to understand the evidence or to determine a fact in issue;
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> (b) the testimony is based on sufficient facts or data;
>
> (c) the testimony is the product of reliable principles and methods; and

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[5] F.R.E. 402.

[6] F.R.E. 401.

[7] *Moore v. Ashland Chemical, Inc.*, 151 F.3d 269, 276 (5th Cir. 1998)(*en banc*).

[8] *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 592, 113 S.Ct. 2786, 2796, 125 L.Ed.2d 469 (1993).

[9] *Id.*, 509 U.S. at 592-93; *Moore*, 151 F.3d at 276.

(d) the expert has reliably applied the principles and methods to the facts of the case.

In the United States Supreme Court's landmark decision in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, the Court acknowledged the existence of a federal courts' gatekeeping role with regard to expert scientific opinion testimony, characterizing that role as one ensuring that such evidence meet the requirements of both reliability and relevance.[10] "Reliability" as discussed in *Daubert* refers to *evidentiary* reliability, *i.e.*, trustworthiness, rather than *scientific* reliability - which asks whether application of the principle produces consistent results - a distinction often blurred by Defendants' arguments. In a case involving scientific evidence, reliability is based upon scientific validity, which asks whether the principle supports what it purports to show.[11]

The objective of this requirement is to make sure that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.[12] The Supreme Court identified several non-exclusive factors a Court should consider in determining whether proffered scientific opinion testimony is sufficiently reliable to permit admission into the record.[13] Those factors are:

- whether the expert's theory can be or has been tested;
- whether the theory has been subject to peer review and publication;
- the known or potential rate of error of a technique or theory when applied;

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[10] *Moore*, 151 F.3d at 275.

[11] *Daubert*, 509 U.S. at 590 n.9.

[12] *Kumho Tire Company, Ltd. v. Carmichael*, 526 U.S. 137, 152, 199 S.Ct. 1167, 1176, 143 L.Ed.2d 238 (1999). *See* also *Brown v. Illinois Cent. R. Co.*, 705 F.3d 531, 535 (5th Cir. 2013).

[13] *See* discussion, 509 U.S. at 594-595.

- the existence and maintenance of standards and controls; and
- the degree to which the technique or theory has been generally accepted in the scientific community.[14]

Several years later, the Supreme Court clarified the inquiry when it held the gatekeeping role applied to all types of expert opinion testimony, not just scientific evidence, and revisited the reliability analysis.[15] Moreover, the Supreme Court reiterated that a court must have considerable leeway in deciding, in a particular case, how to go about determining whether particular expert testimony is reliable.[16] Therefore, the test of reliability is flexible and there is no necessary or exclusive list of factors that must exist in order for a particular opinion to be admissible.[17]

> *Daubert* makes clear that the factors it mentions do not constitute a definitive checklist or test. *Daubert* adds that the gatekeeping inquiry must be tied to the facts of a particular case. We agree with the Solicitor General that the facts identified in *Daubert* may or may not be pertinent in assessing reliability, depending on the nature of the issue, the expert's particular expertise, and the subject of his testimony. The conclusion, in our view, is that we can neither rule out, nor rule in, for all cases and for all time the applicability of the factors mentioned in *Daubert*, nor can we now do so for subsets of case categorized by category of expert or by kind of evidence. Too much depends upon the particular circumstances of the particular case at issue.[18]

In the Fifth Circuit "[t]o determine whether proffered testimony is reliable, the trial court must make 'a preliminary assessment of whether the reasoning or methodology underlying the testimony is . . . valid and of whether that reasoning or methodology properly can be applied to

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[14] *Moore*, 151 F.3d at 275.

[15] *Kumho Tire*, 526 U.S. at 141-142.

[16] *Id.* at 152.

[17] *Id.* at 141-142, 149.

[18] *Id.* at 150 (citations and quotation marks omitted).

the facts in issue.'"[19] Further, "[t]o establish reliability under *Daubert*, an expert bears the burden of furnishing 'some objective, independent validation of [his] methodology.'"[20] In doing so, "[t]he expert's assurances that he has utilized generally accepted [principles] is insufficient."[21]

In *Brown* the Fifth Circuit held that the trial court did not abuse its discretion excluding expert testimony where an expert testified that offered opinions were reliable merely upon and because of "education and experience" and did not engage in or rely upon a credible methodology, particularly in the face of evidence in opposition to those opinions. Standing alone then, it is insufficient for an expert to base his or her opinion on education and experience alone, especially in the face of evidence to the contrary.

In support of their argument, the Defendants invoke what they argue to be the generally-accepted, theory that the Actos® clinical studies cannot demonstrate causation of bladder cancer, and argue that, therefore, the Plaintiffs' theory, and their experts' testimony espousing that theory, should be excluded as it is inconsistent with the agreed generally accepted theory. Plaintiffs, in turn, argue their theory, which they argue is based upon an evolving scientific and medical understanding that pioglitazone can cause or promote cancer in less than one year and thus, their experts should be allowed to testify. First, this Court notes, the *Frye* standard of admissibility suggesting a theory must be generally accepted in the scientific community before it may be presented to a jury has been abrogated in the federal courts.[22] Thus, even where a theory of general causation might not have yet become generally accepted, this Court cannot

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[19] *Brown*, 705 F.3d at 535 (*quoting Daubert*, 588 U.S. at 592-93).

[20] *Id.* at 536 (*quoting Moore*, 151 F.3d at 276).

[21] *Brown*, 705 F.3d at 536 (*quoting Moore*, 151 F.3d at 276).

[22] *Moore*, 151 F.3d at 274.

ignore the more liberal thrust of the applicable Federal Rules of Evidence[23] which argue to allow certain *otherwise reliable* expert opinion testimony to be admitted *if capable of being subject to* "vigorous cross-examination, the presentation of contrary evidence, and careful instruction on the burden of proof,"[24] so as to honor, and not displace, the jury's role in the adversary system.[25]

The Defendants' Motion does not challenge *the relevance* of the challenged testimony, nor the qualifications of the Plaintiffs' experts to develop their opinions. Instead, the Defendants have challenged the reliability and, thus, admissibility of the challenged testimony, primarily within the context of a vigorously-disputed scientific and medical debate among a cadre of otherwise-qualified scientific and medical experts.[26]

II. ANALYSIS

Plaintiffs bear the ultimate burden on this issue, thus, this Court will first look to Plaintiffs' prima facie showing. Pivotal within the theoretical dispute between Plaintiffs and Defendants, in this case, is a set of studies cited by both plaintiffs and defendants in support of their respective theories. Defendants maintain a steadfast adherence to the generally-accepted premise that a cancer of this nature requires at least one year to develop and, consequently, the argued logical sequella that, therefore, any cancers which present within one year must, consequently, be excluded from any statistical analysis and, therefore, cannot carry any statistical

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[23] The Federal Rules of Evidence take a general approach of relaxing the traditional barriers to opinion testimony, *Daubert*, 509 U.S. at 588, and were "designed to depend primarily upon lawyer-adversaries and sensible triers of fact to evaluate conflicts." *Id.* at 589 (citation omitted).

[24] *Daubert*, 509 U.S. at 596.

[25] *U.S. v. 14.38 Acres of Land*, 80 F.3d 1074, 1078 (5th Cir. 1996).

[26] The qualifications of these experts are not challenged in this motion by Defendants, but for Dr. Madigan; certain of the experts, however, are the subject of separate *Daubert* challenges. This Court has reviewed all filings as to those separate motions and does not find, within the challenges made, sufficient question as to those opinions to negatively impact this Court's ruling as to this motion. Full reasons and findings will be provided by this Court as to each of these experts who was the subject of a separate *Daubert* motion.

meaning within those studies. Defendants argue in support of their theory, the very studies Plaintiffs' cite in support of their theory. Plaintiffs maintain steadfast adherence to their argument that the evolved and evolving scientific knowledge, along with many of the same studies used by Defendants, establish Defendants' theory as flawed and self- proving, and argue those cancers which present within one year of exposure must be included in any statistical analysis, and do carry statistical meaning within those studies. Plaintiffs argue Defendants' theory illustrates a narrowness of view and flawed self-sustaining analysis underpinning the, heretofore, generally-accepted premises Defendants so strongly defend and suggest an alternative theory of causation.

Perhaps, at the core of the debate is whether cases of cancer presenting in one year or less from first exposure to pioglitazone, should be excluded from or included within consideration within the pivotal studies. Defendants argue for exclusion – with such exclusion Defendants mount a statically based argument that exposure to pioglitazone cannot cause bladder cancer. Plaintiffs argue for inclusion - with such inclusion Plaintiffs mount a statically based argument that exposure to pioglitazone can cause or promote cancer. Whether one excludes or includes those cases falling within the first year of exposure *keys to the scientific theory of causation* employed and each theory, in turn, keys to whether one includes or excludes those first year cases. It is within this scientific debate that the battle is waged. The matter, however, is further complicated as to both theories by a certain "bootstrapping" at play. Each theory operates upon an assumption which requires exclusion or inclusion and at the same time, it is only, or primarily, by way of the exclusion or inclusion the assumptions are proved. Defendants rely upon a generally accepted theory and assumption; Plaintiffs rely upon an evolving and not yet generally accepted theory and assumption. Which approach is correct or more persuasive will be

for the jury to determine. Whether the jury is to hear Plaintiffs' theory and assumptions, and whether the experts opining as to those theories and assumptions are to be excluded by this Court in its gatekeeper role, is the essence of the motion and inquiry at hand.

In summary, Plaintiffs, in effect, argue a medical significance for/to the cases *excluded* by Defendants from consideration; Defendants argue scientific and medical evidence requires the exclusion of those same cases. In effect, Plaintiffs argue if one refuses to consider those occurrences presenting within one year of exposure, when, in fact, such occurrences have and do occur, one is creating a flawed and self-perpetuating premise, which Plaintiffs' experts believe is flawed. Plaintiffs' experts rely on much of the same scientific evidence as do Defendants, however, the two sets of experts give differing interpretations to the studies. Defendants exclude a certain subset of data, whereas Plaintiffs embrace the same subset of data to grant support for their theory. Defendants now ask this Court, within its gatekeeper role, to exclude Plaintiffs' experts' testimony as to the "one year theory."

The task for this Court within this motion, as the gatekeeper, is to determine whether the Plaintiffs' experts have the necessary qualifications, employ the required process, methodology, rely upon sufficiently sound scientific evidence and comport with the inquiry and factors illustrated by *Daubert*, within their respective areas of expertise so as to be allowed to pass the gatekeeper inquiry.

The specific analysis of this issue will begin with consideration of the Plaintiffs' evidence in support of their prima facie case, and then proceed to consideration of the Defendants' specific challenges.

A. The Plaintiffs' Support For Their Theory Of General Causation

The Plaintiffs, in their Memorandum in Opposition to Defendants' Motion,[27] have provided a thorough description of their experts' theory of general causation as well as the evidence the argument supports.

1. Theory And Evidence

Following is a brief, synthesized version of the quite elaborate tapestry the Plaintiffs' have woven of their theory of general causation and their evidence in support of that theory.

a. The Experts

The Plaintiffs' experts, collectively, build and present an overall theory of general causation again, *as a group*:

- Drs. Schneeweiss and Grossman (both are epidemiologists) are of the opinion substantial evidence exists (from both human and non-human studies) to demonstrate that Actos® can cause bladder cancer within one year.
- Drs. Smith and Panigrahy have developed opinions as to the biological mechanisms by which Actos® can cause bladder cancer, and the relatively short time-frame within such cancer can arise.
- Dr. Southgate similarly has developed opinions as to the biological mechanisms by which Actos® can cause bladder cancer.
- Dr. Delacroix is of the opinion that Actos® creates a risk of bladder cancer, even with short-term use, and that data from the PROactive study (among others) are clinically relevant and suggest that pioglitazone acts as a promoter in patients with pre-existing risk factors for urothelial carcinoma of the bladder.
- Dr. Madigan is a statistician who is of the opinion that proper statistical method requires consideration, in the several studies conducted or analyzed by Takeda, of those people who developed bladder cancer within one year of exposure to Actos®.

[27] Rec. Doc. 3634.

This Court, for these purposes, will look to the challenges made by Defendants and the arguments made by both sides, *within the context of the collective*, as well as Defendants' challenges, if made, to specific aspects of the underpinning of that theory.

b. Tumor Promoter Theory

Plaintiffs admit and agree that long-standing published medical literature pronounces the classic understanding of cancer development and considers it to be a three-stage process: (a) initiation (where irreversible genetic modification occurs in a normal cell, priming the cell for uncontrolled growth); (b) promotion (where initiated cells commence uncontrolled growth); and (c) progression. However, Plaintiffs argue recent peer-reviewed literature demonstrates the scientific and medical communities' understanding of this process as one solely of a simple three-stage process is expanding, and evolving into a more nuanced and more elaborate understanding, which they argue now includes concepts such as cancer stem cells, circulating tumor cells, the tumor microenvironment, and receptor-mediated carcinogenesis. This latter concept is the central premise to the Plaintiffs' theory of causation grounded on the theory of promotion. Specifically, Plaintiffs argue *receptor-mediated cancer* is a process whereby a chemical agent binds to a receptor on the outside of a cell wall, thus changing the way the cell behaves, and Plaintiffs' experts' opine these changes can, also, lead to the development of cancer, or in theory, can increase the rate of growth of a tumor that already exists. It is this theory of "causation" or promotion which Plaintiffs, primarily, argue and Defendants challenge in this motion.

The Plaintiffs have presented evidence they agree demonstrates the underpinning and foundational aspects of the theory of receptor-mediated cancer are scientifically valid. First, in general, Plaintiffs argue *human studies* have demonstrated that hormone replacement therapy in

postmenopausal women affects estrogen receptors, and triggers an increase in breast cancer. Plaintiffs argue this study demonstrates the viability of *the theory* that chemical agents can function as *tumor promoters* in humans. Second, Plaintiffs argue *rodent studies* have shown that PPAR agonists, of which pioglitazone is one, as discussed below, can trigger rapid development of cancer. Plaintiffs argue these studies, among others, support their theory by demonstrating that chemicals agents which behave in the manner as does pioglitazone can serve as tumor promoters in mammals.

It is this theory and its foundational underpinnings Defendants now challenge.

c. Scientific Evidence That Dual PPAR Agonists Behave As Tumor Promoters

The Plaintiffs' argued theory rests predominantly upon the conclusion that pioglitazone is a dual PPAR agonist, i.e. a chemical that binds to two different receptors on the outside of cells, or activator. Plaintiffs have produced peer-reviewed rodent studies demonstrating that pioglitazone is a dual PPAR agonist, and rodent studies demonstrating that dual PPAR agonists have the potential to trigger a number of biological processes, for instance, processes involving PPAR gene expression, changes to the tumor microenvironment that promote tumor growth, promotion of the growth of new blood vessels that supply blood to tumors, etc., any or all of which Plaintiffs argue, through their experts, might be occurring in the presence of pioglitazone.

This Court finds with this evidence, the Plaintiffs have demonstrated sufficient evidence within a prima facie inquiry to meet Defendants' *threshold* challenge as to the prong of scientific evidence of the existence of biological mechanisms that could explain the behavior of pioglitazone as a tumor promoter.

d. Human Studies Showing An Increased Risk Of Bladder Cancer After Exposure to Pioglitazone

The Plaintiffs, also, have produced evidence they argue demonstrates that pioglitazone has been shown in clinical studies to cause bladder cancer. Specifically, the Plaintiffs rely primarily on two clinical trials or studies to support their theory:[28]

- The first, a randomized, placebo-controlled, double-blind clinical trial, known as the ***"PROactive trial"*** which was conducted at the behest of the Defendants. The authors of the study conducted an analysis and concluded there was no evidence supporting a causal link between pioglitazone and bladder cancer. However, the data produced by the authors of the study was published in 2005, and the Plaintiffs' experts have reviewed and re-analyzed that data with a different understanding of the information allegedly revealed by those data. Those Plaintiffs' experts concluded the data *does* support a finding of such a causal connection. The conflict between and among Plaintiffs and Defendants' experts' interpretation of the data, stems from the *inclusion or exclusion* of a certain subset of data – i.e., cases where bladder cancer presented within one year of exposure to pioglitazone – as well as the interpretation and significance of that data. The source of the two different interpretations of the data – and this point is acknowledged by both parties – is Takeda's belief that bladder cancer has such a long latency period that those bladder cancer cases that did develop during the first year of the study *could not* have been caused by pioglitazone and, therefore, the data regarding those cases of cancer should be excluded from consideration. However, the Plaintiffs have produced evidence to argue biological plausibility of a theory that bladder cancer can develop within one year if exposed to a tumor promoter; additionally, the Plaintiffs have produced evidence suggesting pioglitazone is such a tumor promoter, and thus, the cases of bladder cancer which presented within one year should be, at least, considered as data; the scientific significance, or lack thereof, of that data remains a matter of dispute between the two parties' respective cadrés of experts. In light of the evidence, not otherwise shown to be scientifically unreliable, of biological plausibility presented by Plaintiffs, this Court finds that Plaintiffs' interpretation of the PROactive data, although subject to strong attack and vigorous dispute, is sufficiently reliable to overcome Defendant's threshold challenge to Plaintiffs'

[28] The Plaintiffs have included discussion of a third study, known as the KPNC study, which is alleged to have demonstrated a statistically significant doubling of the risk of bladder cancer in patients with cumulative doses ranging from 7,100 to 18,000 mg and suggested the bottom end of this range could be reached within as few as 5 to 7½ months. However, the KPNC study has not yet been completed and must be used very carefully, if at all, in determining the reliability of the Plaintiffs' theory of general causation. In light of this need for caution, and as this Court's decision does not turn on the finality of the KPNC study, this Court will not consider the KPNC study *at this juncture* and will look only to the other studies cited by the Plaintiffs.

prima facie case, and if otherwise admissible, can be presented to the trier of fact, here, the jury.

- The second study – known as the "Hsiao study" – was a nested case-control observational study from the Taiwanese National Health Insurance Research Database. The Hsiao study showed an increase of bladder cancer in exposure with less than one year, one to two years, and more than two years. The study, also, demonstrated an increased risk of bladder cancer with increased duration of exposure, suggesting the study found a dose-response relationship, an argument Defendants seemed to embrace at oral argument, albeit perhaps, with multiple caveats.[29]

As noted, although Defendants argue certain possible weaknesses and flaws and different interpretation of the data within the studies discussed above, Defendants do not establish that the noted studies are so flawed as to be outside consideration by this Court in the gatekeeper task at hand. Consequently, after full review of the Plaintiff's evidence and argument presented, the Court finds the evidence and argument sufficient to support Plaintiffs' prima facie theory of causation.

2. Rule 702/Daubert Factors

This Court now turns its attention to Defendants' challenge to the evidence challenged of the theory itself and its underlying foundational aspects and, therefore, turns the Court's attention to the Daubert factors, and Defendants' challenge based upon those factors. After full review of all argument, evidence and supporting documentation, this Court finds the five factors identified in *Daubert* either weigh in favor of admissibility or do not weigh in favor of exclusion of the challenged evidence.

[29] At oral argument, the Defendants argument inferred a possible recognition that the Hsiao study did report an increased risk of bladder cancer during the first year of exposure to Actos®. However, the argument made lacked sufficient clarity for this Court to definitively discern Defendants' actual position on this, as well as on other points at issue.

- ***Testability***. The Plaintiffs' experts argue each underpinning and foundational aspect of their collective theory of general causation has been tested through the mechanism of clinical trials and other studies and the test results demonstrate support for their theory. Defendants have not presented evidence or argument to invalidate the Plaintiffs' experts' reliance on the underlying tests and studies or of the underlying test and studies themselves. Although the Plaintiffs' theory, itself, has not undergone full testing, the underlying data, tests, and studies relied upon by the experts have. Consequently, this Court finds the testability of the underlying studies and evidence supports a finding of sufficient reliability to overcome threshold challenge. The absence of testing of the theory itself is not fatal when acceptable methodology has been used and the underlying foundational underpinnings have been tested.

- ***Peer Review***. The Plaintiffs' experts have cited to a great many peer-reviewed publications that provide scientific support for each element of their theory of causation; indeed, more than a few of these articles were published by one or more of the Plaintiffs' experts as a result of their study of pioglitazone *before* they were hired as experts in this matter. While it does not appear the collective theory of general causation posed in this matter has been subject to peer-review, unlike *Frye*, *Daubert* does not pivot as strongly on peer review publication. Furthermore, the majority of the underlying publications upon which Plaintiffs experts rely, have been subject to peer review. This Court, also, notes that Plaintiffs' experts, individually, and as a collective, rely heavily on those peer-reviewed publications in formulating their individual as well as their collective opinion. Such reliance upon peer-reviewed publications lends strong support to the reliability of the opinions supported by or drawn from those peer-reviewed publications absent evidence of a flawed methodology within the studies themselves or the manner of reliance upon those studies. Consequently, this Court finds the reliance on peer-reviewed publications lends support to the reliability of the experts' opinions. The absence of peer-review testing of the theory itself is not fatal when acceptable methodology has been used and the underlying foundational underpinnings have been peer-reviewed.

- ***Rate of Error***. Each study relied upon by the Plaintiffs' experts has a rate of error attached to the theory or technique used and those rates of error are available for and subject to vigorous cross-examination. Defendants have not shown any to be wholly without merit or without scientific consequence. The absence of a rate of error as to the collective theory, itself, also, is not fatal in the face of such error rates as to each underlying study.

- ***Standards and Controls***. The Plaintiffs' experts appear, on the face of their qualifications, to be qualified scientists who have conducted their research and developed their opinions in compliance with the standards and controls under which they normally operate in their professional lives. This Court finds that those standards and controls, also, lend support for sufficient reliability of the experts' opinions sufficient to overcome Defendants' threshold challenge on this point.

- ***General Acceptance.*** As noted above, it is not lost on this Court that the Plaintiffs' collective theory that pioglitazone causes or promotes bladder cancer at the rate found by the Plaintiffs' experts has not, at this juncture, been generally accepted in the medical and scientific community. However, this fact, alone, does not so undermine *the reliability* of the experts' opinions when based upon otherwise reliable studies, publications and evidence, as to trigger this Court's gatekeeper function because (a) the experts have openly acknowledged they have developed and argue a new understanding of the mechanisms by which bladder cancer can be promoted; and (b) their actions, conclusions, and opinions have been guided by the scientific method and are sufficiently supported by independent studies and articles within the relevant scientific and medical discipline and communities.

Consequently, this Court finds the Plaintiffs have sufficiently demonstrated the threshold reliability of the underpinning of their theory; that their experts' opinions are sufficiently consistent with the requisite scientific methods and practices used in their normal professional lives; and sufficient reliability of the foundational underpinnings as to overcome Defendants' *threshold* challenge.

3. *Prima Facie* Case

Consequently, this Court has conducted an exhaustive review of the briefs, the exhibits submitted in support of both parties' arguments made within those briefs and argument made at oral argument, and has reviewed all relevant expert reports under challenge. The Court finds, based upon that review, oral argument and for the reasons noted herein and explained at oral argument, that sufficient reliable evidence exists to make a *threshold finding* that the Plaintiffs' experts are universally qualified within their respective fields; they have relied strongly on a standard scientific method of reviewing otherwise reliable scientific evidence and constructing their theory therefrom; their reports demonstrate a strong adherence to the stringent standards they apply in their daily lives as scientists and the foundational underpinnings of their theory, thus, Plaintiffs have met the Defendants' threshold challenge as to reliability. Additionally, this Court notes, that unlike in *Brown*, in the instant matter, the opinions offered are not based solely

on the experts' "education and expertise," rather, are based upon otherwise acceptable underlying publications, studies and evidence. Although the Defendants challenge the Plaintiffs' experts' underlying foundational prongs and conclusions on the basis of contrary evidence, the mere existence of evidence which might be argued inconsistent, does not, in and of itself, render an otherwise arguably properly formulated opinion or study or publication unreliable.

Had the Plaintiffs' experts merely relied on their "education and experience" as did the expert in *Brown*, or completely ignored information in conflict with their opinions, Defendants' argument would be more persuasive, however, that is not the case. Consequently, this Court, also, finds the Plaintiffs' experts' opinions do not fail the threshold test of *Brown* and, thus, the Court will move to the more specific arguments and challenges made by Defendants.

For these and the foregoing reasons noted, this Court finds the Plaintiffs have met their *prima facie* burden of demonstrating their theory of general causation, together with expert testimony through which their theory is to be presented to the jury.

This Court will now turn to the Defendants' specific challenges beyond the prima facie.

B. The Defendants' Challenges

The Defendants have asserted two primary challenges to the Plaintiffs' expert evidence. The first challenge – by far the more significant – is to *the science* of and of *the underpinning* of the Plaintiffs' general causation theory itself; the second is to the testimony of Dr. David Madigan, a statistician. There is no challenge to the Plaintiffs' experts' qualifications generally, nor to the possible relevance of their opinions.

1. The One-Year Requirement

It appears to be uncontested, in this case, that the well-known, well-understood, and generally-accepted mechanisms by which bladder cancer are believed to be caused require more

than one year of exposure to a causative agent before a tumor can develop. On the basis of this generally-accepted scientific knowledge, Takeda's meta-analysis of data derived in 37 clinical studies, as well as its analysis of data derived in the PROactive study, excluded consideration of cases and information concerning those individuals who had developed bladder cancer within the first year of exposure to Actos®.[30] It is uncontested that, once such data was excluded, Takeda was able to reach the conclusion that those clinical studies, without the excluded data, demonstrated no statistically significant increase in bladder cancer among individuals taking pioglitazone.

By contrast, the Plaintiffs' experts consider it improper to exclude from consideration those cases of bladder cancer developed within one year of exposure to pioglitazone, have re-analyzed the data, including those, heretofore, excluded cases, and have concluded that the same clinical studies demonstrate a statistically-significant increase in bladder cancer among individuals exposed to pioglitazone. The Plaintiffs' experts have applied, on their face, established statistical methods, models, and concepts, to the data created by Takeda's clinical studies and have reached a conclusion that is at odds with the conclusion reached by Takeda. There is no evidence or persuasive argument presented, that the conclusions reached, and the theory developed in order to explain those conclusions, are biologically implausible; to the contrary Plaintiffs' experts put forth evidence of biological plausibility – all of which, of course, is vigorously challenged by Defendants. However, in the absence of evidence of biological implausibility and in the face of, albeit vigorously contested, evidence of biological plausibility,

[30] Takeda has, however, acknowledged that the excluded data does have some significance. *See* Memorandum in Support of Motion to Exclude Testimony of Plaintiffs' Experts that Actos® Can Cause Bladder Cancer Within One Year of Use ["Memorandum"] [Rec. Doc. 3466-1], at 9 ("At most, the limited first-year imbalance in these studies suggests that there is a temporal proximity between Actos® exposure and the development of bladder cancer in a very small number of patients.") This recognition and different interpretation, suggests the dispute between the experts is, in fact, the type of scientific argument that is best suited for presentation to the jury and vigorous cross-examination.

the mere fact that the Plaintiffs' theory is new, and in conflict with the status quo, does not, in and of itself, render such evidence or opinion automatically inadmissible as a threshold inquiry if otherwise properly supported and the result of a reliable methodology. As general jurisprudence and accepted logic recognizes, to hold otherwise would, in effect, freeze all theory in place at the status quo and not allow for the natural and necessary progression of knowledge and understanding, scientific or otherwise. As noted above, general acceptance and conventional knowledge no longer provide an absolute measure by which admissibility is determined.[31] To the contrary, the fact that the Plaintiffs' experts used, on their face, established scientific methods and reviewed much of the same evidence, data, and studies as did Defendants, and yet, reached a different conclusion(s) than did Defendants, demonstrates the question at issue is of the type that should be presented to the jury and is not one for the gatekeeper. Plaintiffs have demonstrated the theory and testimony they rely upon to be sufficient for the threshold inquiry at hand, and this Court suggests Defendants' arguments are better directed to a vigorous cross-examination.

The Defendants, however, also, argue two additional specific challenges to the Plaintiffs' evidence in an effort to demonstrate Plaintiffs' theory is unreliable.

a. The use of rodent studies

First, the Defendants challenge the Plaintiffs' and their experts' reliance on rodent studies as a source of information about how pioglitazone functions. Defendants' argue, "Plaintiffs' experts have no evidence in humans to suggest that Actos® acts as a promoter of bladder cancer. The best they can do is extrapolate from a handful of animal studies in which rodents developed

[31] *See Moore*, 151 F.3d at 274.

bladder tumors within a few months of pioglitazone or rosiglitazone exposure under highly artificial conditions."[32]

This Court notes it is clear from the Manual, relied upon by both parties within their argument, epidemiologists often use rodent studies in their efforts to determine causal associations, although such studies are much more commonly used in the closely-related field of toxicology, however, they must do so carefully.[33]

> Where both animal toxicologic and epidemiologic studies are available, no universal rules exist for how to interpret or reconcile them. Careful assessment of the methodological validity and power of the epidemiologic evidence must be undertaken, and the quality of the toxicologic studies and the questions of interspecies extrapolation and dose-response relationship must be considered.[34]

Thus, according to the Manual – again, cited by both parties in their briefs in support of various aspects of their arguments – an experts reliance on rodent studies is neither new or unique to science, but an accepted practice, however, all agree such reliance must be looked at carefully.

The Manual notes the three central tenets on which the toxicologic[35] discipline rests: (a) the dose makes the poison; (b) a chemical agent tends to produce a specific pattern of biological effects; and (c) ***the toxic responses in laboratory animals are useful predictors of toxic responses in humans***.[36] More specifically, qualitative extrapolation in toxicology rests upon the fact that "one can usually rely on the fact that a compound causing an effect in one mammalian

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[32] Memorandum at 7.

[33] REFERENCE MANUAL ON SCIENTIFIC EVIDENCE, at 564-65 (3d ed. 2011) ["MANUAL"] (Reference Guide on Epidemiology).

[34] *Id.*

[35] The discipline of toxicology is primarily concerned with identifying and understanding the adverse effects of external chemical and physical agents on biological systems. MANUAL at 635. The science of toxicology attempts to determine at what doses foreign agents produce their effects. *Id.* at 637.

[36] MANUAL at 636-37.

species will cause it in another species."[37] Thus, according to the Manual, rodent studies are useful – in both epidemiology[38] and toxicology[39] – for assisting a scientist in understanding *potential causal relationships in humans* and possible biological mechanisms of action and reaction in humans. Both epidemiology and toxicology loom large in the scientific debate at hand.

Notwithstanding the guidance contained in the Manual, this Court notes, the Fifth Circuit suggest animal studies, alone, are of limited usefulness in demonstrating that a chemical agent is toxic to humans, *particularly when unaccompanied by evidence of an effect in humans*. In *Brock v. Merrell Dow Pharmaceuticals, Inc.*,[40] the Fifth Circuit noted the very limited usefulness of animal studies under the facts of that case.[41] In *Brock* the Fifth Circuit found the animal studies, which were introduced to prove that Bendectin is a teratogen, were speculative because of methodological flaws,[42] and the inability to extrapolate the results of those particular studies to humans, based on expert admissions.[43] Moreover, the Court found that the reanalysis of a study by plaintiffs' expert on causation was inconclusive as it did not produce a statistical

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[37] MANUAL at 646 (Reference Guide on Toxicology).

[38] Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations. The purpose of epidemiology is to better understand disease causation and to prevent disease in groups of individuals. Epidemiology assumes that disease is not distributed randomly in a group of individuals and that identifiable subgroups, including those exposed to certain agents, are at increased risk of contracting particular disease. MANUAL, at 551.

[39] *See supra* note 35.

[40] *Brock v. Merrell Dow Pharmaceuticals, Inc.*, 874 F.2d 307, 313-14 (5th Cir.), *as amended*, 884 F.2d 166 (5th Cir. 1989).

[41] *Id.*

[42] *Id.* at 313.

[43] *Id.* at 314.

significance.[44] Therefore, lacking any published epidemiologic studies showing a statistically significant effect in humans to support the plaintiffs' underlying theory of causation, *the only remaining scientific evidence in Brock was the animal studies*, which the trial court and Fifth Circuit found, *inter alia*, contained methodological flaws.[45]

A more recent opinion from the Fifth Circuit, *Johnson v. Arkema, Inc.*,[46] again noted the limited usefulness of animal studies standing alone and noted "studies of the effects of chemicals on animals must be carefully qualified in order to have explanatory potential for human beings."[47] In *Johnson* the Fifth Circuit upheld the District Court's rejection of a baboon study where experts admitted the baboon's respiratory tract, the affected portion of the body, and human respiratory tract were different as the human respiratory tract is "pretty unique."[48] Moreover, the expert did not attempt to formulate a correlation between the duration and length of baboon exposure and the Plaintiff's exposure to the agent that caused the particular malady.[49] Finally, the Fifth Circuit noted there were no other animal studies, including other baboon studies that corroborated the one study at issue's conclusions. Therefore, the Court concluded under the "careful qualification" requirement the district court did not abuse its discretion in rejecting the baboon study.

Each of these cases is factually distinguishable from the present case. In the case at hand, the Defendants have not challenged the underlying methodology of the rodent studies, and in the

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[44] *Brock*, 874 F.2d at 313.

[45] *Id.* at 314-315.

[46] *Johnson v. Arkema, Inc.*, 685 F.3d 452, 463 (5th Cir. 2012).

[47] *Id.* at 463 (citing *Allen v. Pa. Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996)).

[48] *Id.*

[49] *Id.*

case at hand, Plaintiffs are not relying solely on rodent studies to prove their theory of causation. The Plaintiffs use the animal study(ies) and data to argue "biological plausibility," and cite human studies – i.e. the breast cancer estrogen studies, to help bridge and build their arguments. This Court recognizes the Fifth Circuit's caution on the use of animal studies and agrees, however, the facts at issue in this case present different scenario than do the cases cited and do not mandate a similar result. Here, Plaintiffs' reliance on animal studies is not the sole evidence relied upon. Additionally, here, the animal studies are not being relied on exclusively to present Plaintiffs' theory, the animal studies--in this case rodent studies--are only but a portion of the evidence relied on by Plaintiffs, which includes human studies to construct their theory and do not use the animal studies alone or directly to prove causation. Therefore, this Court finds, after a review of all evidence presented, which the Plaintiffs' put forth to construct their theory, under the facts of this case, the Plaintiffs' reliance on and use of animal studies is "carefully qualified," as required by the circuit court.

Were it true that the Plaintiffs' experts relied *solely* on rodent studies to establish *causation* in humans – as the Defendants' arguments seem to suggest, but which Plaintiffs' evidence proves otherwise – this Court would have greater concern[50] and would find Defendants' argument more persuasive, however, as noted, that is not the case.

b. Clinical Studies are not reliable

Next, the Defendants challenge the reliability of the two human clinical studies upon which the Plaintiffs' experts, also, rely.

[50] The Fifth Circuit takes the position that animal studies are of limited usefulness in demonstrating that a chemical agent is toxic to humans, particularly when unaccompanied by evidence of an effect in humans. *See, e.g., Johnson*, 685 F.3d at 463-64; *Brock*, 874 F.2d at 313-14, *as amended.* 884 F.2d 166 (5th Cir. 1989).

The PROactive Clinical Trial. The parties agree the PROactive Clinical Trial was well-designed, and its execution is not under challenge. As noted above, the Plaintiffs' experts rely upon the PROactive study, and interpret the PROactive data as confirming a causal association between pioglitazone and bladder cancer. The Defendants rely on the PROactive study and interpret the PROactive data as disproving a causal association between pioglitazone and bladder cancer. Again, the dispute centers upon data originating from those cases which presented within one year of exposure – whether those cases should be excluded – as Defendants argue, or included – as Plaintiffs argue. Defendants argue, in part, Plaintiffs' challenged experts' conclusions based upon consideration of those cases within one year of exposure, are not reliable because those experts cannot *prove* the bladder cancers that occurred during the first year of the PROactive study were, in fact, caused by Actos®. This argument suggests a misapprehension of the nature of epidemiological studies and the legal requirement at hand, which this Court finds perplexing given the sophistication of Defendants' counsel. Within the discipline of epidemiology, it is neither necessary, or appropriate, nor is it likely, possible for an epidemiologist to determine the *actual cause* of any given subject's illness particularly *before* employing that data in an epidemiological study to determine the possible association, if any: an epidemiological study is conducted for the purpose of obtaining data with which to evaluate *whether* a causal association likely exists or likely does not exist. To argue one must require a scientist to *prove causation* in order to use data in an epidemiological inquiry, it would seem, would render the exercise of conducting an epidemiological study meaningless. Consequently, this Court does not find Defendants' argument on this point persuasive.

Additionally, experts are not limited to using only those epidemiological studies in which they can *prove* all, or any, of the individuals, here, bladder cancers were *actually caused* by a

given exposure, here, to Actos®; to mount such an argument would seem at its very best, disingenuous. Epidemiological studies are *designed to generate statistical data* in support of *the scientific effort to determine* what, if anything, that data might reveal about a possible causative relationship or association, here, between Actos® and any side effects that might come to light during the study. It would not be appropriate to use, nor do Plaintiffs' experts attempt to use, the Defendants' epidemiological study to attempt to make findings as to *specific causation in a particular study subject*, nor is it appropriate to argue one must know the desired result of data found within a study *before engaging in the very study* designed to determine *if there is a given association at play*. Again, this Court finds Defendants' argument on this point wholly unpersuasive.

The Hsiao Study. The Defendants challenge the Hsiao study as unreliable, and thus, Plaintiffs' experts' reliance on that study fatally flawed, arguing it is an observational study and, therefore, cannot establish either specific causation or the biological mechanisms by which Actos® is alleged to cause bladder cancer.[51] Once again, the Defendants' argument is founded on what seems to be, at best, a misunderstanding and, at worst, a very questionable characterization of the nature of observational studies, the type of information that can be derived from that type of study and Plaintiffs' actual use of the challenged study, and thus, is unpersuasive.

First, the implicit suggestion in the Defendants' argument that the Plaintiffs used the Hsiao study to determine *specific causation* or biological mechanisms would seem to be, at best, misleading as a review of the Plaintiffs' experts' reports and opinions reveals Plaintiffs' experts do neither.

[51] *See supra* note 29.

Next, the Defendants, also, imply the Hsiao study is inconsistent with other studies conducted in Taiwan using subsets of the same data and thus, Plaintiffs' experts' reliance on that study is flawed and thus, Plaintiffs' theory must fail. This argument ignores other evidence presented and relied upon by Plaintiffs' experts and the evidence presented that the Hsiao study is, in fact, distinguishable from the other Taiwanese studies. Whether the Hsiao study is distinguishable, as Plaintiffs' experts argue, or inconsistent, as Defendants argue, is a question for cross-examination and not exclusion. When, as here, the Plaintiffs' experts admit the existence of the studies argued by Defendants, have evaluated those studies, have chosen not to consider those studies, and most significantly, have fully explained their analysis, decisions, and the reasons for those choices, the proper remedy is vigorous cross-examination. The mere fact other studies might or might not argue for or against the results of a given study or opinion given and the fact that certain studies have or have not been embraced, but were considered by an expert, does not, in and of itself, render the experts' opinions so flawed as to mandate exclusion, rather merely invites vigorous cross-examination.

No Single Study Answers All Questions. During oral argument, counsel for the defense asserted that the Plaintiffs' theory of causation is unreliable because it has "never been shown to occur." Upon this Court's request for clarification, it became evident the Defendants suggest the Plaintiffs' *theory* is not reliable – and should not be allowed to be relied upon by the jury – because there is no *one study* that has demonstrated the causal link between Actos® and bladder cancer. This argument was not made explicitly in the Defendants' briefs, and at oral argument, argument to explain, or demonstrate, how or why a scientific theory must be demonstrated with *one single study* was not given. However, nowhere has this Court heard or seen, on the part of the Defendants, argument or evidence to explain why a given theory must be deemed wholly

unreliable merely because it requires multiple steps to prove, particularly if each of those steps cannot be shown to be unreliable in and of themselves, and if a proper scientific methodology was employed, by otherwise qualified experts in their respective fields. Neither has this Court found jurisprudence from its independent review suggesting such a limitation of expert opinion testimony that is otherwise grounded in sound scientific methodology and evidence. Defendants' argument on this point, also, is not persuasive.

c. Latency period

The Defendants' final challenge to the Plaintiffs' general theory of causation argues the Plaintiffs' experts' opinions should be excluded because the experts have no opinion as to the latency period required for bladder cancer to develop under their theory of causation.[52] Other than baldly declaring this failure and, again, baldly asserting this alleged failure must render the Plaintiffs' theory "pure conjecture," the Defendants have not explained or provided jurisprudential or factual support for their argument that the Plaintiffs' theory *must include* a definitive latency period in order to be reliable. Rather, and to the contrary, it would seem, the dispute at issue is one which focuses, in no small part, upon latency periods and the bases for those opinions as to latency periods, and what data should and should not be considered to establish the proper latency period and given the "proper" latency and developmental periods, which data should and should not be considered. Notwithstanding the lack of factual or jurisprudential support for this quite weak argument, out of an abundance of caution, this Court conducted independent research in the Manual,[53] as well as in the jurisprudence, and found no support for Defendants' weak and, arguably, circular argument that the Plaintiffs' expert's

[52] Memorandum, at 11-12.

[53] REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (3d ed. 2011).

opinion(s) and testimony is so unreliable as to be inadmissible absent a definitive latency period having been espoused, when the relevant latency period is a central aspect of the scientific dispute at hand.

2. Dr. David Madigan

The Defendants, also, seek to preclude Dr. David Madigan from testifying that Actos® can cause bladder cancer "to develop" within one year of first exposure, however, do not point to where, within his report, Dr. Madigan sets forth any such opinion. Nonetheless, given the importance of the issues at hand, this Court, again, searched through Dr. Madigan's report and his testimony *and found no indication that Dr. Madigan has formed any opinion as to how long it takes for bladder cancer to develop*. Furthermore, the Plaintiffs have demonstrated they have no intention of asking Dr. Madigan to opine as to the length of time after exposure to Actos® that bladder cancer can or does develop. Once again, it would seem, Defendants' have erected a strawman argument only for the purpose of forcing Plaintiffs, and the Court, to expend the time and the energy to knock it down. Defendants have no other identifiable challenge to Dr. Madigan.

III. EVIDENTIARY HEARING

The Defendants had requested this Court agree to hear live testimony from the experts prior to ruling on the instant motion, and this Court carefully considered the Defendants' request. However, the decision of how to go about ruling on the instant motion is squarely within this Court's discretion.

> The trial court must have the same kind of latitude in deciding *how* to test an expert's reliability, and to decide whether and when special briefing or other proceedings are needed to investigate reliability, as it enjoys when it decides whether or not that expert's relevant testimony is reliable. Our opinion in *Joiner* makes clear that a court of appeals is to apply an abuse-of-discretion standard when it reviews a trial court's decision to admit or exclude expert

> testimony. That standard applies as much to the trial court's decisions about how to determine reliability as to its ultimate conclusion. Otherwise, the trial judge would lack the discretionary authority needed both to avoid unnecessary "reliability" proceedings in ordinary cases where the liability of an expert's methods is properly taken for granted, and to require appropriate proceedings in the less usual or more complex cases where cause for questioning the expert's reliability arises. Indeed, the Rules seek to avoid unjustifiable expense and delay as part of their search for truth and the just determination of proceedings.[54]

This Court reviewed the extensive briefing provided by both parties, as well as the large number of exhibits, including expert reports, depositions, and other documents, and concluded the nature of the challenges presented and the arguments made did not illustrate the need for live testimony. Live testimony would not likely contribute to any greater understanding of the nature of the dispute than could be found in a careful reading and analysis of the briefs and accompanying evidence and documentation. The request for an opportunity to present live testimony in an evidentiary hearing is DENIED. However, in recognition of the importance of these issues to both the Defendants' and Plaintiffs' cases, this Court allowed oral argument[55] and conducted full oral argument on December 12, 2013. Consequently, this Court hereby incorporates into the instant ruling this Court's comments and explanations reflected in the Transcript of Oral Argument heard on December 12, 2013. Defendants, also, have filed a *Daubert* challenge of Plaintiffs' expert, Dr. David Delacroix; within that argument, Defendants, again, challenge Plaintiffs' experts as to general causation. To the extent this Court addressed Defendants' challenge to general causation within its ruling as to Defendants' *Daubert* motion

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[54] *Kumho Tire*, 526 U.S. at 152-53 (emphasis in original) (citations and quotations omitted).

[55] Although it appeared at oral argument as though the Defendants intended to amend or at least attempt to expand their motion to seek alternative relief, the Defendants' final word indicated they did not. However, this Court was and remains quite perplexed as to the contrast between the arguments made and relief requested within the submitted briefs, and the arguments and relief requested at oral argument. Such seeming contradictory conduct within Defense counsel was and remains both perplexing and disturbing to the Court.

on Dr. Delacroix, this Court hereby adopts and incorporates herein the discussion and ruling made within that motion *as to general causation*.

CONCLUSION

Although, difficult to clarify, Defendants seem to pose a two prong challenge to Plaintiffs' experts. First, to the overall theory itself as lacking in peer review and testability and certain other of the *Daubert* factors, and next to the individual underpinnings of that theory lacking sufficient scientific reliability. Nonetheless, for the reasons noted herein, addressed in the ruling in the Delacroix motion, and articulated at oral argument had on December 12, 2013 – all adopted and incorporated herein, this Court finds neither prong, nor do both prongs if considered in tandem, require removing the opinions of Plaintiffs' experts from consideration from the jury. Although, perhaps, fodder for vigorous cross-examination, Plaintiffs' experts' opinions survive the threshold challenge mounted by Defendants for the full reasons noted.

For the foregoing reasons, the Defendants' Motion to Exclude Testimony of Plaintiffs' Experts that Actos® Can Cause Bladder Cancer Within One Year of Use [Rec. Doc. 3466] shall be DENIED.

THUS DONE AND SIGNED this 19 day of December, 2013.

REBECCA F. DOHERTY
UNITED STATES DISTRICT JUDGE